## *Remarks*

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-6 are pending in the application, with 1 being the independent claim. Support for the amendment to claim 1 is found in the specification at page 1, line 35. Support for the amendment to claim 6 is found in the claims as originally filed. No new matter is added by these amendments.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

***Rejections under 35 U.S.C. § 112***

Claims 1-6 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. (Office Action, page 2). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that:

> [t]he term LSI as recited in claims 1-3 and 5-6 is indefinite because the metes and bounds are unclear. Additionally, art recognized definitions for LSI include things other than integrated circuits, for example although the specification breathes life into the meaning it does not limit the claims. The term LSI as defined in the specification at page 1, line 35 defines LSI as a "large scale integrated circuit", however, there is no limitation as to the metes and bounds of the term "large" which is a relative term and as such is indefinite.

(Office Action, page 2). Applicants respectfully disagree.

The metes and bounds of the term LSI are not indefinite as there is an art recognized definition of the term as referring to highly integrated circuits in general, and, one of skill in the art would readily recognize that a LSI includes integrated circuits (ICs) having 1,000 to several millions of elements per chip.

An IC was first produced in the 1950s. After that, integration degree rapidly increased due to the progress of technology. In accordance with the improvement in integration degree, ICs have gone though several name changes as "SSI (small-scale integration)" and "MSI (medium-scale integration)," and became known as "LSI (Large-Scale Integration)" in the 1970s. In the 1980s, terms such as "VLSI (very large-scale integration)" having hundreds of thousands of elements and "ULSI (Ultra large-scale integration)" having several millions of elements were sometimes used in the commercial field to refer to ICs with a high density and high integration degree. In those days, the term "LSI" meant ICs having 3,000-100,000 elements per chip.

Forty years have passed since the publication of "Moore's law". However, the law still applies to element integration today, and is thought to predict the improvements of semiconductor performance. In addition, in view of the rapid development of nanotechnology since the late 1990s, such ICs that were once referred to as "VLSI" or "ULSI" come to be collectively called "LSI" in the 21$^{st}$ century.

This art-recognized definition for LSI as encompassing 1,000 to several million elements is evidenced by a reading of dictionaries of computer-related terms. A look at an English translation of the Japanese on-line dictionary of computer terms

(http://www2.nsknet.or.jp/~azuma/i/i0022.htm) for definitions related to the integration degree of ICs finds the following.

> Small Scale Integration (SSI): 100 or fewer elements are fabricated on a single semiconductor chip.
>
> Medium Scale Integration (SSI): 100 to 1,000 elements are fabricated on a single semiconductor chip.
>
> Large Scale Integration (LSI): Integrated circuits having 1,000 to 100,000 elements integrated on a single semiconductor chip. Typically, integrated circuits produced during the 1970s correspond to this. Though the majority is MOS LSI that needs little electricity to work, bipolar LSI has also been developed. As to memory ICs, DRAM greater than the standard of 16 Kbit corresponds to this, and the lower limit of element size (also called the design rule) is within about five micrometers. Today, a more microscopic design rule is adopted. In producing LSIs, accurate processing techniques such as microfabrication by photolithographic technique, dry etching, ion implantation, or such are utilized.
>
> Very Large Scale Integration (VLSI): Semiconductors having 100,000 to 10,000,000 elements are integrated on a single chip. Typically, integrated circuits produced during the 1980s or later correspond to this. In general, however, the term "LSI" is often used to collectively refer to this.
>
> Ultra Large Scale Integration (ULSI): Semiconductors having 10,000,000 or more elements are integrated on a single chip. In general, however, the term "LSI" is often used to collectively refer to this.

The following English translation of the definition for LSI is found in the "glossary for IT terms" (http://e-words.jp/w/LSI.html).

> Large Scale Integration: IC that has element integration degree between approximately 1,000 and 100,000. Or, simply a synonym of IC. This term was created during the 1970s to distinctively refer to techniques and/or products with infinitely higher integration degree as compared to early ICs. However, in these days, "LSI" is used as a word that simply refers to semiconductor integrated circuits in general, as the term "IC" does. After the 1970s, there was a time when ICs having integration degree over 100,000 and 10,000,000 were distinguished as "VLSI" and "ULSI", respectively. However, after moving into the 21st century, such distinction has become rarely used.

As can be seen by the definitions in two separate dictionaries specific for the art in question, the term LSI has an art-recognized definition as an IC having an integration degree of about 1,000 up to 10 million or more. Although "100,000 elements per chip"

was the upper limit settled on for the term LSI from the technical standard of the 1970s, one skilled in the art can readily understand that chips having several millions of elements are well within the scope of today's LSI, in view of the progress of technology brought on by nanotechnology. Further, the Examiner has provided no evidence to show that one of skill in the art would not understand the scope of the term LSI or would consider LSI to encompass "things other than integrated circuits" when read in light of the specification. Thus, the metes and bounds of the term are clear and the claim is not indefinite.

Claim 5 has been rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. (Office Action, page 2). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that:

> [c]laim 5 is indefinite for failing to clearly set the metes and bounds of the term "mediates" because the process by which an antibody "mediates" the binding of a protein is unclear. Is the antibody linked to the substrate? Does the antibody directly or indirectly "mediate" the binding of the protein?

(Office Action, page 2). Applicants respectfully disagree.

It is clear from a reading of the specification that the present invention encompasses both direct and indirect binding of nucleic acids or proteins to the LSI (see page 3, lines 22-23). Claim 5, in which an antibody bound to the protein mediates binding of the protein to the LSI, therefore encompasses both direct and indirect binding between the antibody and the LSI. In other words, when an antibody is used to bind a

protein to an LSI, the antibody binds to both the protein and the LSI (or a substrate on the LSI), thus interconnecting the protein and the LSI. While the claim encompasses multiple types of linkages between the antibody and the LSI, breadth alone does not make a claim indefinite. M.P.E.P. 2173.04.

Claim 6 has been rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. (Office Action, page 2). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the limitation "a sugar chain of the protein" in line 1 lacks sufficient antecedent basis. (Office Action, page 2). Applicants respectfully disagree.

Claim 6 as amended does not require antecedent basis for the phrase "a sugar chain of the protein." Thus, the claim is not indefinite.

Applicants respectfully submit that the Examiner's stated grounds for rejection have been accommodated and it is respectfully requested that the rejection of claims 1-6 under 35 U.S.C. § 112, second paragraph be withdrawn.

***Rejections under 35 U.S.C. § 102***

Claims 1-3 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Mandecki (U.S. Patent No. 6,046,003). (Office Action, page 3). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that:

> [r]egarding claim 1, Mandecki teaches a method for producing a labeled nucleic acid (e.g., fluorescently-

> labeled target DNA bound to probe attached to the surface of the transponder), wherein the method comprises binding the nucleic acid (e.g., oligonucleotides) to a large scale integrated circuit (e.g., solid phase particles having a transponder associated with each particle), and recording specific information (e.g., the sequence of the oligonucleotide) on the large scale integrated circuit (column 1, lines 55-coloumn 2, line 6; column 17, lines 28-44).
>
> Regarding claim 1, Mandecki teaches a method for producing a labeled protein (e.g., protein-nucleic acid) wherein the method comprises binding the protein to a large scale integrated, and recording specific information on the large scale integrated circuit (Column 3, lines 25-27).
>
> Regarding claim 2, Mandecki teaches wherein the specific information is characteristic to the nucleic acid (e.g., the sequence of the oligonucleotide ) bound to the LSI (column 1, lines 58-60).
>
> Regarding claim 3, Mandecki teaches a method wherein a substrate (e.g., monoisocyanate) mediates the binding of a nucleic acid to the large scale integrated circuit (column 8, lines 21-45).

(Office Action, page 3). Applicants respectfully disagree.

As a basis to reject novelty of a method for producing a labeled protein, the Examiner cites the description at column 3, line 25-27 listing PNA (protein-nucleic acid) as an example of molecules to be immobilized on a transponder. Contrary to the Examiner's assertion, Applicants submit that PNA is not a protein but an analog of nucleic acids. PNA stand for "polyamide nucleic acid", which is also called "peptide nucleic acid" or "protein nucleic acid." PNA has a similar structure to that of a polynucleotide, but its backbone to which the bases are attached comprises peptide-like amide bonds. Furthermore, Mandecki himself describes PNA as an example of a nucleic acid, not a protein (column 3, line 25-27). Since Mandecki fails to disclose a method for

producing a labeled protein, reconsideration and withdrawal of this rejection is respectfully requested.

With regard to a method for producing a labeled nucleic acid, Applicants submit that the method described in Mandecki comprises direct chemical synthesis of the oligonucleotide on the transponders. The only example of immobilizing DNA probes on particles relies on the chemical synthesis of the oligonucleotide probe directly on the particle (see Example 1). While Mandecki mentions the possibility of conjugation of oligonucleotides to the particle (column 3, lines 36-40), no details are provided on how to accomplish this and no examples are provided. Mandecki therefore does not enable one of skill in the art to directly bind presynthesized or purified oligonucleotides to a particle.

On the other hand, the method claimed in the present invention comprises binding a presynthesized or purified nucleic acid or protein to an LSI. This is clear from the recited step in claim 1 of "binding the nucleic acid or protein to an LSI." This binding step can be carried out, for example, by adding a presynthesized or purified nucleic acid or protein on an LSI to which a substrate is attached. As the present method for producing a labeled nucleic acid does not require direct chemical synthesis steps, it is clearly distinguishable from the method of Mandecki.

Further, Mandecki teaches nucleic acids bound to solid phase particles wherein a transponder is associated with each particle (column 1, lines 55-60). In contrast, the present invention is drawn to a method comprising binding the nucleic acid or protein to an LSI. While the binding between the nucleic acid or protein and the LSI may be direct or indirect, indirect binding does not encompass an embodiment wherein a nucleic acid

and an LSI are each attached to the same solid phase particle as this does not constitute binding of the nucleic acid to the LSI.

Claim 3 requires that a substrate mediate the binding of the nucleic acid or protein to the LSI. The Examiner states that Mandecki teaches the use of monoisocyanate as a substrate mediating the binding the nucleic acid to the particle. However, Mandecki actually discloses a monoisocyanate derivative of thymidine as the first nucleotide bound to the particle during the process of synthesizing an oligonucleotide on the particle (column 8, lines 21-30). Thus, there is no substrate mediating the binding of the oligonucleotide to the particle.

Mandecki does not disclose each element of the claimed invention. Thus, Mandecki does not anticipate claims 1-3. It is respectfully requested that the rejection of claims 1-3 over Mandecki be withdrawn.

Claims 1 and 3-5 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Gordon *et al.* (U.S. Patent No. 6,251,595). (Office Action, page 4). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that:

> [r]egarding claim 1, Gordon et al teach a method for producing a labeled (e.g., electronically addressed, column 6, lines 15-17) nucleic acid, wherein the method comprises binding the nucleic acid (e.g., oligonucleotides) to a large scale integrated circuit (e.g., electrode assembly; column 18, lines 1-65; column 14, lines 36-49; Fig. 2), and recording specific information on the large scale integrated circuit (column 5, lines 19-22).
>
> Regarding claim 1, Gordon et al teach a method for producing a labeled (e.g., electronically addressed, column 6, lines 15-17) protein, wherein the method comprises binding the protein (e.g., enzymes, column 11, lines 51-60) to a large scale integrated circuit (e.g., electrode assembly; column 18, lines 1-65; column 14, lines 36-49; Fig. 2), and

> recording specific information on the large scale integrated circuit (column 5, lines 19-22).
>
> Regarding claim 3, Gordon et al teach a method wherein a substrate (e.g., cellulosic materials and materials derived from cellulose) mediates the binding of a nucleic acid or protein to the large scale integrated circuit (column 9, lines 35-40).
>
> Regarding claim 4, Gordon et al teach a method wherein a cellulose vinyl acetate (e.g., cellulosic materials and materials derived from cellulose) mediates the binding of a nucleic acid or protein to the large scale integrated circuit (column 9, lines 35-40).
>
> Regarding claim 5, Gordon et al teach a method wherein an antibody bound to a protein mediates the binding of protein to the large scale integrated circuit (e.g., antigen-antibody, column 11, lines 51-63).

(Office Action, page 4). Applicants respectfully disagree.

Gordon *et al.* disclose methods and devices for carrying out multiple chemical reactions (column 5, lines 13-31). The methods comprise the steps of directly synthesizing an oligonucleotide or an oligopeptide on a semiconductor substrate that carries a large-scale integrated circuit. Specifically, the method of Gordon *et al.* produces nucleic acids/proteins bound to semiconductor substrate by (i) placing a plurality of electrodes supported by a semiconductor substrate in proximity with a reaction medium, which comprises reagents for carrying out the chemical reactions, (ii) selectively applying electric signals to each of the electrodes, and (iii) carrying out a chemical reaction proximal to and in response to the field at the electrodes to which the electric signals are selectively applied to produce an oligonucleotide/oligopeptide. Other chemical reactions that are disclosed in Gordon *et al.* include conjugating reporter groups or labels to nucleic acids or proteins and diagnostic procedures involving antibody-antigen or antibody-hapten binding (column 11, lines 50-66).

In contrast, the present method binds a presynthesized or purified nucleic acid or protein to an LSI, for example, by adding a presynthesized or purified nucleic acid or protein on an LSI to which a substrate is attached. As the present method for producing a labeled nucleic acid or protein does not require direct chemical synthesis steps, it is clearly distinguishable from the method of Gordon *et al.*

Gordon *et al.* do not disclose each element of the claimed invention. Thus, Gordon *et al.* do not anticipate claims 1 and 3-5. It is respectfully requested that the rejection of claims 1 and 3-5 over Gordon *et al.* be withdrawn.

***Rejections under 35 U.S.C. § 103***

Claim 6 has been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Mandecki in view of Keogh (U.S. Patent No. 5,728,420). (Office Action, page 5). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that:

> [r]egarding claim 6, Mandecki teaches a method for producing a labeled nucleic acid (e.g., fluorescently-labeled target DNA bound to probe attached to the surface of the transponder), wherein the method comprises binding the nucleic acid (e.g., oligonucleotides) to a large scale integrated circuit (e.g., solid phase particles having a transponder associated with each particle), and recording specific information (e.g., the sequence of the oligonucleotide) on the large scale integrated circuit (column 1, lines 55-coloumn 2, line 6; column 17 lines 28-44). Mandecki does not teach wherein a sugar chain of the protein is attached to the LSI, and a characteristic of the sugar chain of the protein is described on the LSI.
>
> This concept, the attachment of a sugar chain of a protein to a substrate, however, was well known in the art. Specifically, Keogh teaches a sugar chain of the protein (e.g., glycoproteins) is attached to a substrate (column 3 line 36-column 4, line 13) for the advantage of preventing

> conformational changes in said protein (column 5, lines 1-13). Thus Keogh teaches the composition and provides a clear motivation to bind protein for the use of labeling as binding to the sugar moiety allows the protein to function in it's known and expected ways.
>
> Keogh is seen to meet all limitations of the claim because attachment of the sugar chain protein to the substrate is seen to encompass both directly and indirectly mediate linkage. Therefore, the combination of Mandecki and Keogh is seen to encompass the claimed invention.
>
> Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of Mandeci and Keogh to attach a protein via a sugar chain of said protein to the LSI, and to describe a characteristic of said sugar chain of said protein on the LSI. One of ordinary skill would have been motivated to do so for the advantage of preventing conformational changes in said protein (column 5, lines 1-13).

(Office Action, page 5). Applicants respectfully disagree.

As discussed in above, Mandecki only discloses a method for producing a labeled nucleic acid by directly synthesizing an oligonucleotide on a solid support, and fails to disclose a method for producing a labeled protein. Thus, even if the teachings of Mandecki and Keogh are combined, one of ordinary skill in the art can not reach the method of claim 6 that produces a labeled protein by (1) binding the protein to an LSI via its sugar chain, and (2) recording a characteristic of the sugar chain of the protein on the LSI.

Further, Keogh fails to disclose the recording of a characteristic of the sugar chain of the protein. Keogh also fails to provide any motivation to combine the two references. The Examiner's opinion that Keogh teaches an advantage of preventing conformational changes in the bound protein is incorrect. What Keogh in fact discloses is that bound glycoproteins are susceptible to conformational changes if the substrate

surface is hydrophobic and that this must be taken into account by creating a hydrophilic environment on the substrate surface (column 5, lines 1-25).

Thus, the obviousness rejection based on the combination of Mandecki and Keogh is improper. It is respectfully requested that the rejection of claim 6 over Mandecki in view of Keogh be withdrawn.

## *Conclusion*

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Date: June 15, 2005

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